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Original Article

# Radiation-induced long-term dysphagia in survivors of head and neck cancer and association with dose-volume parameters

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ABSTRACT

*Background:* Although dysphagia is a common side effect after radiotherapy (RT) of head and neck cancer (HNC), data on long-term dysphagia is scarce. We aimed to 1) compare radiation dose parameters in HNC survivors with and without dysphagia, 2) investigate factors associated with long-term dysphagia and its possible impact on health-related quality of life (HRQoL), and 3) investigate how our data agree with existing NTCP models.
*Methods:* This cross-sectional study conducted in 2018–2020, included HNC survivors treated in 2007–2013. Participants attended a one-day examination in hospital and filled in patient questionnaires. Dysphagia was measured with the EORTC QLQ-H&N35 swallowing scale. Toxicity was scored with CTCAE v.4. We contoured swallowing organs at risk (SWOAR) on RT plans, calculated dose-volume histograms (DVHs), performed logistic regression analyses and tested our data in established NTCP models.
*Results:* Of the 239 participants, 75 (31%) reported dysphagia. Compared to survivors without dysphagia, this group had reduced HRQoL and the DVHs for infrahyoid SWOAR were significantly shifted to the right. Long-term dysphagia was associated with age (OR 1.07, 95% CI 1.03–1.10), female sex (OR 2.75, 95% CI 1.45–5.21), and mean dose to middle pharyngeal constrictor muscle (MD-MPCM) (OR 1.06, 95% CI 1.03–1.09). NTCP models overall underestimated the risk of long-term dysphagia.
*Conclusions:* Long-term dysphagia was associated with higher age, being female, and high MD-MPCM. Doses to distally located SWOAR seemed to be risk factors. Existing NTCP models do not sufficiently predict long-term dysphagia. Further efforts are needed to reduce the prevalence and consequences of this late effect.

## Introduction

In head and neck cancer (HNC), late effects are commonly defined as side effects that occur or persist more than three months post-treatment [1,2]. Dysphagia is one of the most serious late effects following radiotherapy (RT) in HNC [3,4], and may impact survivors' health-related quality of life (HRQoL) [5,6]. It can lead to changes in meal routines, malnutrition, feeding tube dependence, aspiration-related airway infections, psychological distress, and social isolation [4,5,7,8]. Information about the impact of long-term (> 5 years) dysphagia is scarce, as the literature primarily addresses the first years post-treatment [9–11]. The improved survival of HNC patients [12] highlights the need for more knowledge about their late effects.

The swallowing function is complex and involves interactions between multiple structures including swallowing muscles and cranial nerves [3,8,10] that are commonly exposed to high RT doses due to

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proximity to the target volumes [6]. Mounting evidence demonstrates that high RT doses to pharyngeal constrictor muscles (PCM), larynx, and oral cavity are associated with dysphagia [5,13–16] that may be irreversible or even progressive over time [17,18].

Normal tissue complication probability (NTCP) models are used to estimate risk of radiation-induced toxicities [19]. They are designed using statistical methods to select relevant explanatory variables, e.g. dosimetric, treatment-related, and clinical factors. To date, the inclusion of patient-reported outcome measures (PROMs) in NTCP modelling has been limited [19].

The purpose of the current study was to provide information on long-term dysphagia in HNC survivors. We aimed to 1) describe the level of long-term patient-reported dysphagia and compare RT dose parameters in HNC survivors with and without dysphagia, 2) investigate factors associated with dysphagia more than five years post-treatment and describe the possible impact on HNC survivors' HRQoL, and 3) investigate how our data agree with existing NTCP models.

## Materials and methods

### *Study design and participants*

The current study was a part of a comprehensive cross-sectional study conducted at Oslo University Hospital (OUH), Norway, over a two-year period from 2018 to provide more knowledge on late effects in HNC survivors beyond five years post-treatment. This was initiated in response to HNC survivors who pointed out the need for such knowledge. Eligible candidates were survivors treated for HNC in the period 2007–2013, $\geq$ 18 years old at the time of survey, and able to attend a one-day visit at OUH. We identified candidates from the hospital registry and invited them to participate by mail. Other sub-studies are published elsewhere [20,21]. The original sample size was based on other long-term effects than dysphagia, aiming inclusion of 280 survivors. Of 310 survivors that consented to participation, 239 were available for analyses in this sub-study (Fig. 1).

### *Data collection*

The participants completed a set of PROMs at home including the European Organisation for Research and Treatment of Cancer Quality of Life core questionnaire (EORTC QLQ-C30) [22] and the HNC specific module (EORTC QLQ-H&N35) [23], before attending the one-day visit. Clinical data including comorbidity according to Charlson comorbidity index [24] and performance status were obtained from clinical examinations during the visit and from medical records and radiation registry systems. Clinicians rated toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0 [25].

### *Treatment*

The primary RT regimen was 2 Gy per fraction, five to six days a week, with a total dose of 70 Gy to tumour and lymph node metastases and 46 Gy to elective neck with concomitant nimorazole, a hypoxic radiosensitizer, in line with DAHANCA guidelines [26]. Patients $<$ 70 years with locally advanced disease received weekly cisplatin 40 mg/m$^2$. In the postoperative setting, patients received 50–66 Gy, 2 Gy per fraction, to the tumour bed(s) and 46 Gy to the elective neck, five days a week, with or without weekly cisplatin [20].

### *Treatment planning and delivery*

Planning CT was performed with the patient immobilised with thermoplastic mask in treatment position. Treatment planning was done in Oncentra Masterplan (v3.0–4.3). At that time spinal cord, parotid

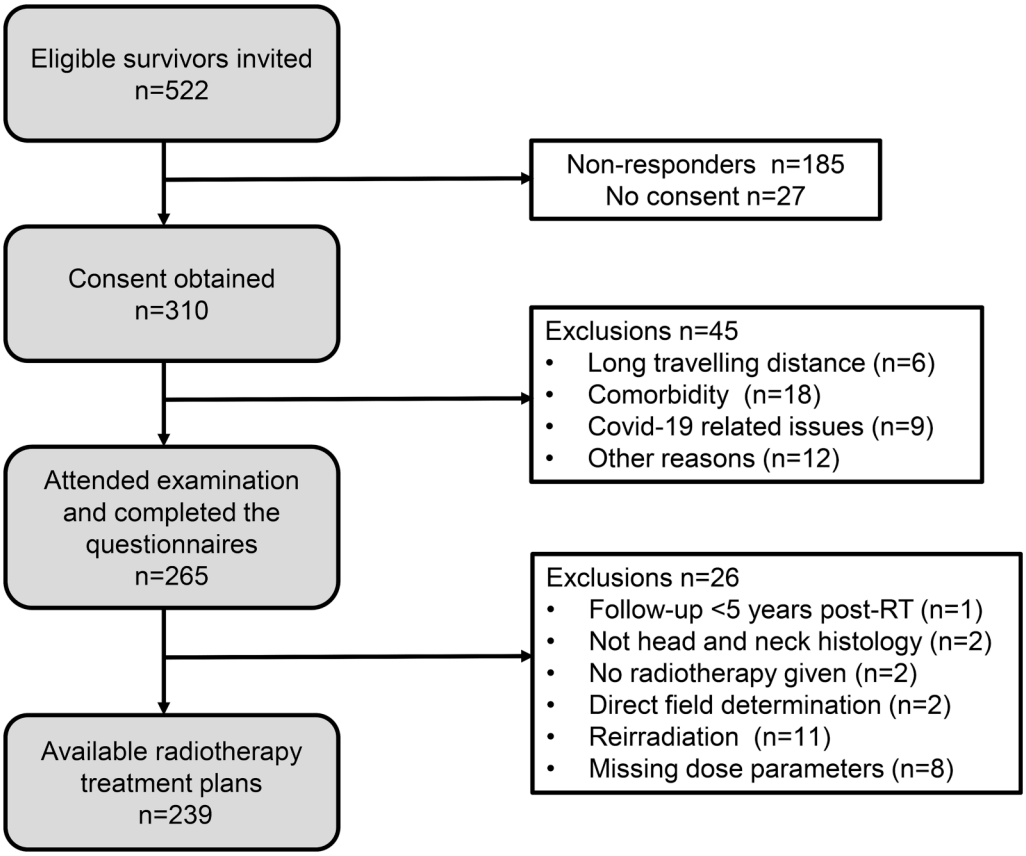



**Fig. 1.** Flowchart of the study participant selection.

glands, and submandibular glands were routinely delineated as organs at risk. Patients were treated with three-dimensional conformal RT or intensity-modulated RT (IMRT) 6 MV photons.

*Swallowing organs at risk and dose-volume parameters*

We exported the treatment plans from Oncentra Masterplan and restored them in Raystation (v11A, RaySearch Laboratories AB, Stockholm, Sweden). Thereafter, we delineated swallowing organs at risk (SWOAR) according to guidelines [27]. Base of tongue (BOT), oral cavity, and superior PCM were defined as suprahyoid SWOAR, while middle PCM, inferior PCM, cricopharyngeal muscle (CPM), esophageal inlet muscle (EIM), supraglottic larynx (SGL), and glottic larynx (GL) were defined as infrahyoid SWOAR. The SWOAR dose-volume parameters were retrieved from Raystation.

*Definition of dysphagia and health-related quality of life*

Patient-reported dysphagia was measured with the EORTC QLQ-H&N35 swallowing (SW) scale consisting of four items; problems swallowing liquids, soft food, solid food, and with choking while swallowing. Each item is scored on a Likert scale with categories 1 (not at all), 2 (a little), 3 (quite a bit), and 4 (very much) that are transformed to a continuous scale score from 0 to 100. High scores indicate high level of dysphagia. In this study, for aims 1 and 2, based on clinical judgement, dysphagia was defined as SW scale score of $\geq 25$ upfront as a scale score of 25 required responses "very much" on at least one of the four SW scale items or "a little/quite a bit" on two or three of the items. For aim 3, to harmonise with Christianen [28], the four items were evaluated separately with responses "quite a bit" or "very much" defined as dysphagia. Observer-rated dysphagia was defined as CTCAE v.4.0 grade $\geq 2$. Dysphagia more than five years post-treatment was defined as long-term dysphagia. Impact of dysphagia on HRQoL was measured with EORTC QLQ-C30 Global QoL scale and the five functional scales (physical, role, cognitive, emotional, and social) [29]. Mean differences of $\geq 10$ points were considered clinically significant [30].

*Statistical analysis*

Descriptive statistics were presented as median and range or mean and standard deviation for continuous data, and as frequency and proportion for categorical data. To compare RT parameters of SWOAR between participants with and without dysphagia, we generated dose-volume histograms (DVHs) with mean values (%) of V5-V70 (in 5 Gy increments) and 95 % confidence intervals (CI). Point estimates with non-overlapping CIs were considered statistically significant. Logistic regression analyses were performed to identify factors associated with long-term dysphagia. Age at RT, sex, comorbidity, smoking status, tumour site, T-stage, N-stage, RT scheme, RT technique, neck irradiation, concurrent chemotherapy, and mean doses to SWOAR were included. Variables with $p < 0.1$ in univariable analyses were included in the multivariable analyses. The number of survivors with dysphagia ($n = 75$) allowed seven variables in the multivariable model using the 1:10 rule-of-thumb [31]. Backward stepwise elimination was performed by removing the least significant variable (highest p-value) at each step, stopping at threshold $p < 0.05$ and results were presented as odds ratios (OR) with 95 % CI. Spearman correlation coefficient was calculated to explore correlations between variables and selection of surrogates was based on variance inflation factor (VIF) to avoid multicollinearity. Regression analyses were also carried out in the subgroup of patients with oropharyngeal cancer. Sensitivity analyses were performed with dysphagia threshold set to EORTC QLQ-H&N35 SW scale $\geq 33$.

To investigate how our data fit with selected NTCP models, we performed a closed testing procedure as described by Vergouwe [32]. Christianen et al [28] and Langendijk et al [33] assessed observer-rated dysphagia (RTOG/EORTC Radiation Morbidity Scoring Criteria and CTCAE, respectively), while Christianen also evaluated patient-reported dysphagia on EORTC QLQ-H&N35 SW scale's four items separately. For each model, one of four methods was suggested based on bootstrapping frequency distribution; 1) keeping the original model (no adjustments), 2) recalibration in the large (only the model intercept is adjusted), 3) recalibration (both the model intercept and slope are adjusted), or 4) model revision (the regression coefficients of all model predictors are re-estimated). The model performance and discriminative ability were tested using Brier Score (BS) and area under the curve (AUC), where values of 0–0.25 and $> 0.7$, respectively, were acceptable [34–36]. Calibration plots for original and updated models were generated to compare model predictions. The participants were binned into 10 equally sized groups, with the fraction of dysphagia per group shown on the y-axis and the predictive risk on the x-axis. We performed statistical analyses in Stata version 17 and R version 4.2.1.

## Results

Characteristics of the overall group, and for HNC survivors with or without long-term dysphagia are displayed in Table 1. All participants completed the PROMs and had received RT with total dose of 50–70 Gy. The participants were compared to non-participating survivors (Supplementary Table 1). Of the 239 survivors included, 75 (31 %) reported dysphagia, and only 9 % of these and 3 % of the overall cohort had percutaneous endoscopic gastrostomy. The participants with dysphagia mainly reported problems with swallowing solid food (68 %) and choking (67 %) (Supplementary Table 2). Details on dysphagia mean score are provided in Supplementary Fig. 1. Fifty-one survivors (21 %) had observer-rated dysphagia (Supplementary Table 3).

Compared to survivors without dysphagia, the DVHs for survivors with long-term dysphagia were shifted more to the right for the infrahyoid SWOAR, indicating a dose-volume effect (Fig. 2). There were no observed differences for the suprahyoid SWOAR.

In the multivariable analyses, middle PCM and EIM were included as surrogates for the other infrahyoid SWOAR to avoid multicollinearity. This was based on the correlation matrix and VIF (Supplementary Table 4) showing strong correlation between mean dose to the middle PCM and inferior PCM and SGL, and strong correlation between mean dose to EIM and inferior PCM, CPM, SGL, and GL. Also, middle PCM and EIM are anatomically distanced. The multivariable analyses identified age at RT (OR 1.07, 95 % CI 1.03–1.10), female sex (OR 2.75, 95 % CI 1.45–5.21), and mean dose to middle PCM (OR 1.06, 95 % CI 1.03–1.09) as significantly associated with long-term dysphagia, while RT scheme, RT technique, neck irradiation, and mean dose to EIM were not (Table 2). Restricted to oropharyngeal cancer ($n = 127$), no association between long-term dysphagia and selected variables was shown (Supplementary Table 5). The sensitivity analyses (cut-off $\geq 33$) gave similar results (Supplementary Table 6) as in the overall cohort. Survivors of HNC with dysphagia cut-off $\geq 25$ had clinically significantly worse mean score of Global QoL, Physical, Role, Emotional, Cognitive, and Social Functioning compared to those without dysphagia (Supplementary Table 7).

The results from the closed testing showed which updated method was suggested for each NTCP model (Supplementary Tables 8–13). It resulted in full revision of Christianen's model 1 (AUC 0.72, BS 0.15) for observer-rated dysphagia and of model 3 (AUC 0.72, BS 0.04) for patient-reported problems with swallowing soft food. The original model 2 (AUC 0.66, BS 0.15) for problems with swallowing liquids and model 6 (AUC 0.63, BS 0.16) for observer-rated dysphagia by Langendijk were suggested to be maintained. The closed testing led to recalibration of model 4 (AUC 0.64, BS 0.17) for problems with swallowing solid food and for model 5 (AUC 0.67, BS 0.17) for choking while swallowing. Calibration plots for both original and updated NTCP models generally indicated suboptimal fit with our data (Fig. 3). They showed some improvement in the revised model 1, where superior PCM was eliminated and resulted in SGL as a sole predictor (Supplementary

**Table 1**
Patient and treatment characteristics of long-term head and neck cancer survivors treated with radiotherapy.

| | All patients n = 239 | No dysphagia n = 164 | Dysphagia[a] n = 75 |
|---|---|---|---|
| **Age at radiotherapy (years)** | | | |
| Median (range) | 56 (14–80) | 55 (14–77) | 60 (35–80) |
| **Age at survey (years)** | | | |
| Median (range) | 65 (20–87) | 64 (20–84) | 69 (43–87) |
| **Time from radiotherapy to survey (years)** | 8.4 (5–13) | 8.4 (5–13) | 8.5 (5–13) |
| Median (range) | | | |
| **CHARACTERISTICS AT THE TIME OF THE SURVEY** | | | |
| **Sex, n (%)** | | | |
| Male | 159 (67) | 116 (71) | 43 (57) |
| **Performance status, n (%)** | | | |
| WHO 0 | 145 (61) | 111 (68) | 34 (45) |
| WHO 1 | 69 (29) | 43 (26) | 26 (35) |
| WHO ≥ 2 | 25 (10) | 10 (6) | 15 (20) |
| **Charlson comorbidity index, n (%)** | 124 (52) | 89 (54) | 35 (47) |
| Score 0 | 115 (48) | 75 (46) | 40 (53) |
| Score 1–8 | | | |
| **Living situation, n (%)** | | | |
| Alone | 57 (24) | 34 (21) | 23 (31) |
| Not alone | 182 (76) | 130 (79) | 52 (69) |
| **Smoking status, n (%)** | | | |
| Never | 67 (28) | 50 (30) | 17 (23) |
| Former | 131 (55) | 89 (54) | 42 (56) |
| Current | 41 (17) | 25 (15) | 16 (21) |
| **Pack years**[b] | | | |
| Median (range) | 8 (0–112) | 7 (0–112) | 12 (0–60) |
| **Current alcohol use frequency, n (%)** | 30 (13) | 15 (9) | 15 (20) |
| Never | 50 (21) | 32 (20) | 18 (24) |
| Monthly or less | 55 (23) | 38 (23) | 17 (23) |
| 2–4 times/month | 79 (33) | 60 (37) | 19 (25) |
| 2–3 times/week | 225 (10) | 19 (12) | 6 (8) |
| 4–5 times/week | | | |
| **Feeding tube, n (%)** | | | |
| Nasogastric tube | 0 (0) | 0 (0) | 0 (0) |
| Percutaneous endoscopic gastrostomy | 7 (3) | 0 (0) | 7 (9) |
| **Dysphagia CTCAE grade ≥ 2, n (%)** | 51 (21) | 11 (7) | 40 (53) |
| **TUMOUR AND TREATMENT CHARACTERISTICS AT THE TIME OF TREATMENT** | | | |
| **Tumour site, n (%)** | | | |
| Oropharynx | 127 (53) | 90 (55) | 37 (49) |
| Nasopharynx | 7 (3) | 2 (1) | 5 (7) |
| Hypopharynx | 4 (2) | 1 (1) | 3 (4) |
| Larynx | 15 (6) | 6 (4) | 9 (12) |
| Oral cavity | 41 (17) | 29 (18) | 12 (16) |
| Nose, sinuses | 7 (3) | 6 (4) | 1 (1) |
| Unknown primary | 12 (5) | 9 (5) | 3 (4) |
| Others[c] | 26 (11) | 21 (13) | 5 (7) |
| **T-stage, n (%)** | | | |
| T0-2 | 184 (77) | 129 (79) | 55 (73) |
| T3-4 | 55 (23) | 35 (21) | 20 (27) |
| **N-stage, n (%)** | | | |
| N0-1 | 126 (53) | 86 (52) | 40 (53) |
| N2-3 | 113 (47) | 78 (48) | 35 (47) |
| **Histology, n (%)** | | | |
| Squamous cell carcinoma | 203 (85) | 137 (84) | 66 (88) |
| Salivary gland carcinomas | 25 (10) | 20 (12) | 5 (7) |
| Undifferentiated carcinoma | 8 (3) | 4 (2) | 4 (5) |
| Others[d] | 3 (1) | 3 (2) | 0 (0) |
| **HPV status, n (%)** | | | |
| No | 29 (12) | 21 (13) | 8 (11) |
| Yes | 67 (28) | 48 (29) | 19 (25) |
| Unknown | 143 (60) | 95 (58) | 48 (64) |
| **Cancer status, n (%)** | | | |
| Recurrence free after primary treatment | 212 (89) | 147 (90) | 65 (87) |
| Treated locoregional relapse | 12 (5) | 8 (5) | 4 (5) |
| Treated second primary | 15 (6) | 9 (5) | 6 (8) |
| **Radiotherapy scheme, n (%)** | 151 (63) | 96 (59) | 55 (73) |
| Primary radiotherapy | 80 (33) | 62 (38) | 18 (24) |
| Postoperative radiotherapy | 8 (4) | 6 (4) | 2 (3) |
| Radiotherapy at relapse | | | |
| **Radiotherapy technique, n (%)** | 131 (55) | 84 (51) | 47 (63) |
| IMRT | 108 (45) | 80 (49) | 28 (37) |
| 3DCRT | | | |
| **Neck irradiation, n (%)** | | | |
| Bilateral | 166 (69) | 105 (64) | 61 (81) |
| Unilateral | 57 (24) | 44 (27) | 13 (17) |
| No | 16 (7) | 15 (9) | 1 (1) |
| **Swallowing organs at risk mean dose, Gy (SD)** | | | |
| Base of tongue | 49 (16) | 48 (16) | 51 (15) |
| Oral cavity | 31 (15) | 31 (15) | 32 (17) |
| Superior PCM | 45 (15) | 44 (15) | 46 (15) |
| Middle PCM | 50 (14) | 47 (15) | 55 (10) |
| Inferior PCM | 41 (16) | 38 (15) | 47 (15) |
| Cricopharyngeal muscle | 34 (16) | 32 (15) | 40 (16) |
| Esophageal inlet muscle | 23 (15) | 21 (14) | 29 (15) |
| Supraglottic larynx | 46 (16) | 43 (16) | 52 (14) |
| Glottic larynx | 36 (18) | 33 (16) | 42 (18) |
| **Concurrent chemotherapy, n (%)** | 124 (52) | 83 (51) | 41 (55) |
| **Nimorazole, n (%)** | 146 (61) | 94 (57) | 52 (69) |

Abbrevations: WHO; World Health Organization, CTCAE; Common Terminology Criteria for Adverse Events, IMRT; Intensity-modulated radiotherapy, 3DCRT; Three-dimensional conformal radiotherapy, SD; Standard deviation, PCM; Pharyngeal constrictor muscle.

[a] Patient-reported dysphagia was defined as cut-off ≥ 25 on European Organisation for Research and Treatment of Cancer Quality of Life core questionnaire, the head and neck specific module, swallowing scale.

[b] Pack years: (number of cigarettes x number of years)/20. For both former and current smokers.

[c] Includes primary site in salivary glands and lip.

[d] Adenocarcinoma/carcinoma with endocrine differentiation.

Table 8). For the remaining updated models 3, 4, and 5, no meaningful improvement was detected on the calibration plots. The risk of underestimating long-term dysphagia was most pronounced for models 4 and 5. The bootstrapping showed uncertainty in the selection of updating methods for these models (Supplementary Tables 11 and 12).

## Discussion

This study provides information to fill the knowledge gap regarding long-term dysphagia in survivors of HNC. The result that one third of the survivors experienced long-term dysphagia with significant negative impact on their HRQoL emphasises the importance of addressing this problem. By studying RT dose parameters involved, identifying possible associations and testing our data on existing NTCP models, we contribute to the ongoing work of reducing the risk of long-term dysphagia in survivors. To our knowledge, this is the first attempt to evaluate whether established NTCP models are suitable for predicting dysphagia more than five years after RT. Our data suggested that higher age, being female, and RT mean doses to infrahyoid SWOAR are associated with long-term dysphagia. Established NTCP models did not sufficiently predict the risk of long-term dysphagia, even after model adjustments in the present study. Our results differ from recent reports with externally validated models. They found the oral cavity to be one of the most important structures discriminating patients with and without dysphagia at six months post-treatment [16,33]. One possible explanation may be the difference in assessment time between the studies and that the dose to the oral cavity might be less important for long-term dysphagia.

The prevalence of long-term dysphagia of 31 % in this study differs

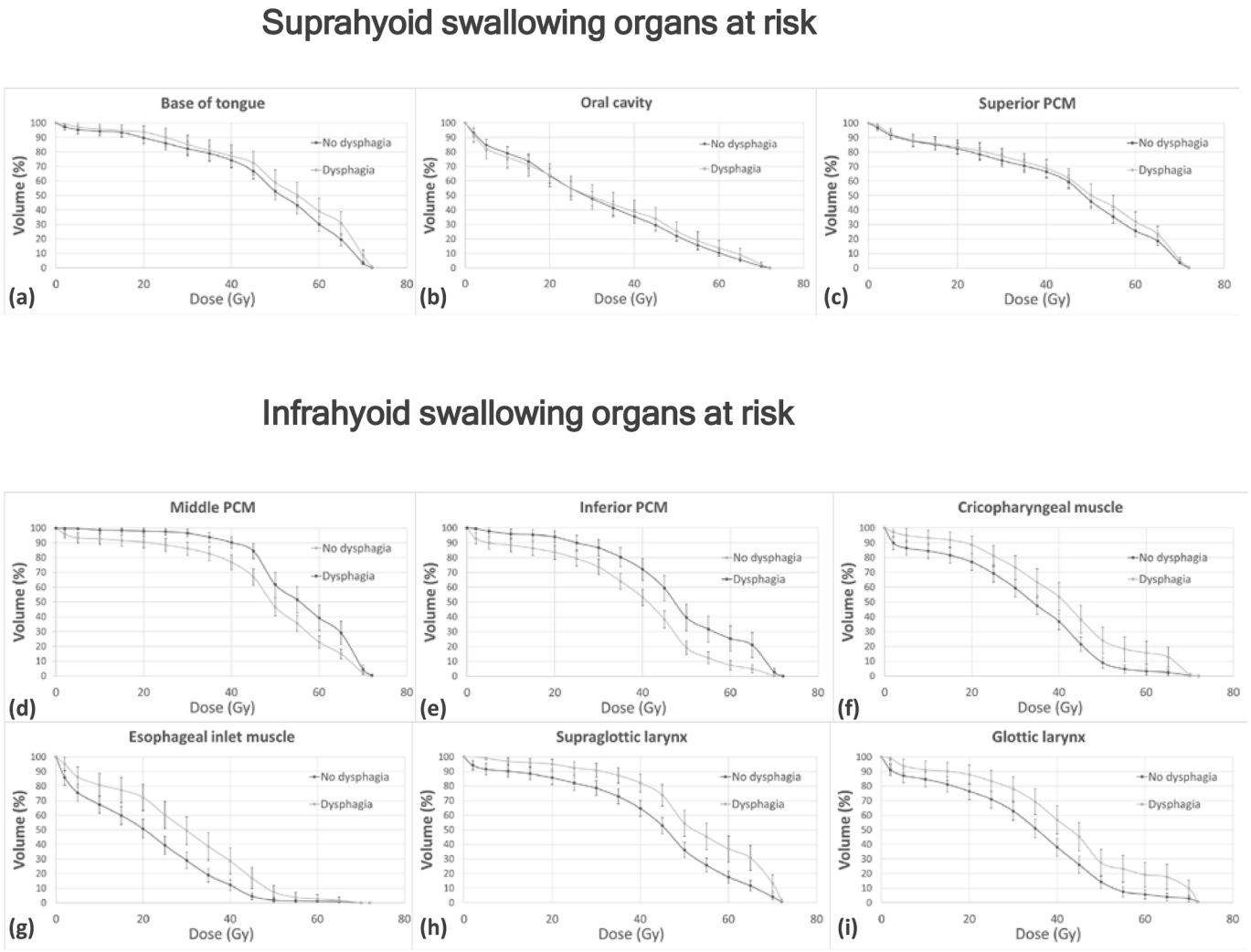



**Fig. 2.** Dose-volume histograms of swallowing organs at risk, stratified by survivors of head and neck cancer with dysphagia (n = 75) and without dysphagia (n = 164). Error bars represent 95 % confidence interval. (a) Base of tongue, (b) Oral cavity, (c) Superior pharyngeal constructor muscle (PCM), (d) Middle PCM, (e) Inferior PCM, (f) Cricopharyngeal muscle, (g) Esophageal inlet muscle, (h) Supraglottic larynx and (i) Glottic larynx.

somewhat from what others have reported. In a study of 148 patients with oropharyngeal cancer and median follow-up of 30 months, 18 % of the participants reported "poor" swallowing function on the M.D. Anderson dysphagia inventory composite score, while only 4 % had dysphagia CTCAE grade $\geq$ 2 [37]. In a population-level analysis of 16 000 HNC survivors, the two-year dysphagia prevalence and the dysphagia-related diagnoses stricture and aspiration pneumonia was 45.3 %, 10.2 %, and 8.7 %, respectively [38]. Another study found that 26 % of HNC survivors had a dysphagia-related diagnosis beyond 5 years follow-up [39]. In general, it was difficult to compare our result with others due to different evaluation methods and assessment time points applied across studies. Instrumental registrations of swallowing have been considered gold standards [6,8], but they are, like observer-rated side effects, found to not sufficiently reflect the patient's symptoms [40–42]. PROMs have therefore gained more impact as study endpoints [14,43,44], although comparison between studies are still challenging as many different PROMs are used to assess dysphagia.

Previous studies indicated dysphagia to be associated with PCM, superior PCM, SGL, and/or GL, but did not show clear distinction between "upper" and "lower" swallowing structures as we found [13,17,45,46]. We observed DVH differences in survivors with long-term dysphagia compared to those without for infrahyoid SWOAR, but not for suprahyoid SWOAR, which deviate with prior reports. Whether this finding has implications for treatment planning needs to be validated for long-term dysphagia in further prospective studies.

The identification of age as an associated factor with long-term dysphagia was in line with previous studies that found increased risk of dysphagia with higher age in HNC survivors [47,48]. RT-induced tissue fibrosis and atrophy have been described as contributive elements of dysphagia, and tend to worsen with older age [49]. This vulnerability may be explained by comorbidity and reduced reserve capacity [50]. Being female was another factor associated with long-term dysphagia, which is in concordance with reports of Orlandi et al [37], but they could not find prior examples in the literature. In reference populations of PROMs, females generally reported more symptoms and more impaired HRQoL than male participants [51]. One could expect this to be transferable to patient cohorts. Middle PCM, as predictor of long-term dysphagia, was considered to represent the other infrahyoid SWOAR due to the high correlation found between these structures. In the regression analyses, we chose to apply mean doses of the SWOAR as covariates, and the results of univariable analyses turned out to comply with the patterns of DVH for the respective SWOAR. This supports earlier publications which found mean doses to SWOAR to correlate strongly with their partial volume doses [28,52]. The subgroup analyses of oropharyngeal cancer show that dysphagia was not associated with the mean doses to the SWOAR. However, this subgroup was relatively small, and the results should be interpreted with caution due to the lack of statistical power.

**Table 2**
Logistic regression analyses of factors associated with long-term dysphagia[a] in survivors of head and neck cancer.

| | Univariable analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95 % CI | p-value | OR | 95 % CI | p-value |
| Age at radiotherapy (years) | **1.059** | **1.024–1.094** | **0.001** | **1.065** | **1.028–1.103** | **0.001** |
| Sex (female vs. male) | **1.798** | **1.019–3.174** | **0.043** | **2.747** | **1.448–5.210** | **0.002** |
| Charlson comorbidity index (≥1 vs. 0) | 1.356 | 0.784–2.346 | 0.276 | | | |
| Smoking status | | | | | | |
| never | Ref. | | | | | |
| former | 1.388 | 0.716–2.689 | 0.331 | | | |
| current | 1.882 | 0.817–4.337 | 0.137 | | | |
| Tumour site (oropharynx vs. other) | 0.801 | 0.463–1.384 | 0.426 | | | |
| T-stage (T3-4 vs. T0-2) | 1.340 | 0.711–2.526 | 0.280 | | | |
| N-stage (N2-3 vs. N0-1) | 0.965 | 0.558–1.668 | 0.898 | | | |
| Radiotherapy scheme | | | | | | |
| Primary radiotherapy | Ref. | | | | | |
| Postoperative radiotherapy | **0.507** | **0.272–0.948** | **0.032** | | | |
| Radiotherapy at relapse | 0.582 | 0.114–2.982 | 0.516 | | | |
| Radiotherapy technique (IMRT vs. 3DCRT) | **1.599** | **0.914–2.796** | **0.100** | | | |
| Neck irradiation | | | | | | |
| Bilateral | Ref. | | | | | |
| Unilateral | **0.509** | **0.254–1.019** | **0.056** | | | |
| No | **0.115** | **0.015–0.890** | **0.038** | | | |
| Concurrent chemotherapy (yes vs. no) | 1.177 | 0.680–2.036 | 0.560 | | | |
| Base of tongue, mean dose (Gy) | 1.013 | 0.995–1.032 | 0.165 | | | |
| Oral cavity, mean dose (Gy) | 1.004 | 0.986–1.022 | 0.651 | | | |
| Superior PCM, mean dose (Gy) | 1.009 | 0.990–1.028 | 0.373 | | | |
| Middle PCM, mean dose (Gy) | **1.052** | **1.024–1.082** | **<0.001** | **1.060** | **1.028–1.093** | **<0.001** |
| Inferior PCM, mean dose (Gy) | **1.047** | **1.025–1.070** | **<0.001** | | | |
| Cricopharyngeal muscle, mean dose (Gy) | **1.036** | **1.016–1.056** | **<0.001** | | | |
| Esophageal inlet muscle, mean dose (Gy) | **1.040** | **1.019–1.061** | **<0.001** | | | |
| Supraglottic larynx, mean dose (Gy) | **1.045** | **1.023–1.068** | **<0.001** | | | |
| Glottic larynx, mean dose (Gy) | **1.032** | **1.014–1.050** | **<0.001** | | | |

Abbreviations: OR; Odds ratio, CI; Confidence interval, IMRT; Intensity-modulated radiotherapy, 3DCRT; Three-dimensional conformal radiotherapy, PCM; Pharyngeal constrictor muscle.
Bold: Univariable analyses $p < 0.1$; Multivariable analyses $p < 0.05$.
[a] Patient-reported dysphagia was defined as cut-off ≥ 25 on European Organisation for Research and Treatment of Cancer Quality of Life core questionnaire, the head and neck specific module, swallowing scale.

Adaption to symptoms may be expected many years following treatment [53,54], but the present study showed that dysphagia post five years follow-up was negatively associated with the survivors' HRQoL and their physical, emotional, and social functioning. Swallowing is a basic function, and even minor deviations might influence general health, well-being, and contentment [11,41]. Swallowing activity can also be negatively influenced by other radiation-induced symptoms such as xerostomia, dysgeusia, trismus, and lymphedema. These late effects can also contribute to deteriorated HRQoL and functioning [17].

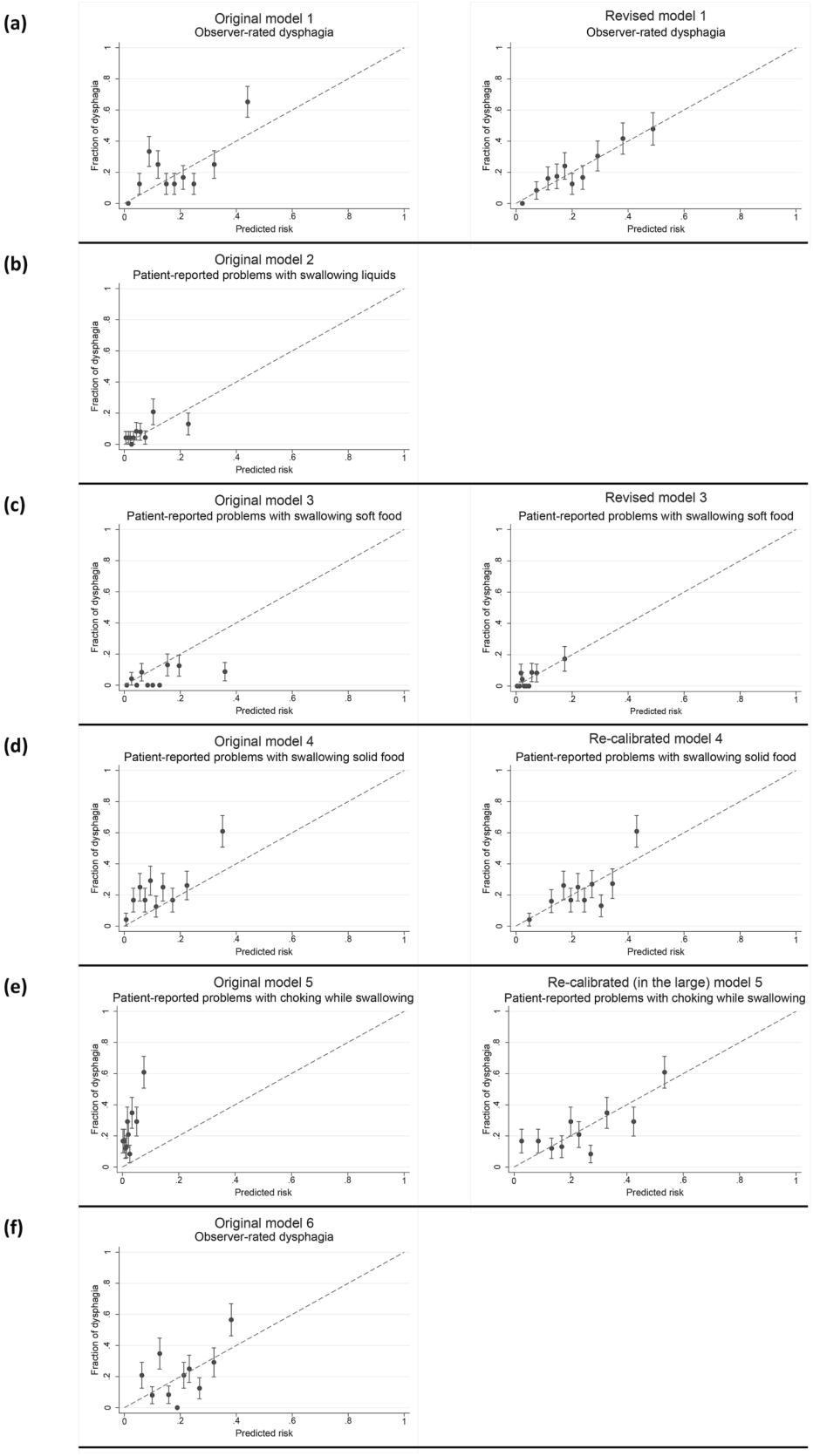
The updated NTCP models based on our data mostly had acceptable AUC and BS, but overall the calibration plots showed a poor fit, mainly exhibiting risk underestimation. This finding supports the point made by Van Calster et al [55] that models with good discrimination can be poorly calibrated, and thereby be misleading in clinical decision-making. Disagreement due to the difference in time of assessment can also be related to fibrosis and atrophy of SWOAR, which may occur or progress years after treatment completion leading to long-term dysphagia [17,56,57]. However, knowledge of underlying biological mechanisms of dysphagia and progression over time is yet insufficient. Hansen et al [58] emphasized that the study cohort and the validation cohort should be as similar as possible when evaluating NTCP models, as differences can give deviating model factors and parameters. Christianen et al [28] did not report the frequencies of observer-rated and patient-reported dysphagia, leaving us unaware of their numbers compared to ours. The present study results highlight the need for NTCP models which predict long-term dysphagia, preferably in prospectively collected data, where optimal calibration and validation processes are warranted.

SWOAR sparing strategies have been introduced in recent years showing promising results in reducing toxicity [59,60]. Still, we believe our results of previous treatment practices are relevant in prioritising OAR in dose-sparing strategies of today's treatment planning and in improving NTCP models for long-term dysphagia.

This study is strengthened by the high compliance and use of PROMs, as the survivors' own experience of dysphagia more directly reflects how this impact their daily lives. However, defining dysphagia as EORTC QLQ-H&N35 SW scale score of ≥ 25 may be questioned. This was based on careful consideration of the possible responses of the four items of the SW scale and we performed a sensitivity analysis that supported this definition. The cross-sectional design is another limitation as baseline data were not available. Baseline swallowing function has been reported as an independent predictor of dysphagia [4,9]. Our study included a more heterogeneous cohort compared to others, who primarily limit inclusions to patients with squamous cell carcinomas of the pharynx, oral cavity, and larynx treated in a primary setting. However, the purpose of our study was to describe the clinical reality. When comparing the participants to the non-participating survivors, there were no difference in sex or travel distance to the hospital, but there was a difference in age. The age distribution of the participants ranged from 20 to 87 years, while non-participating survivors had an age range of 16–97 years. A selection bias is possible, because survivors with high level of symptoms might regard participation more meaningful than those without complaints, or the opposite; survivors with high level of symptoms might find the one-day visit too tiresome.

## Conclusions

The present study found that one third of the HNC survivors experienced long-term dysphagia with significant negative impact on their HRQoL. Our data suggested that higher age, being female, and RT mean doses to infrahyoid SWOAR are associated with long-term dysphagia.




(caption on next page)

**Fig. 3.** Calibration plots for original and updated normal tissue complication probability models. (a) Model 1: Observer-rated dysphagia by Christianen et al, original and revised, (b) Model 2: Patient-reported problems with swallowing liquids, original, (c) Model 3: Patient-reported problems with swallowing soft food, original and revised, (d) Model 4: Patient-reported problems with swallowing solid food, original and re-calibrated, (e) Model 5: Patient-reported problems with choking while swallowing, original and re-calibrated, (f) Model 6: Observer-rated dysphagia by Langendijk et al, original. Dashed lines represent perfect match, where the intercept has the value 0 and slope has the value 1. Generally, curves or points which lie above this line underestimate the predicted risk, and conversely, curves and points below the line overestimate the predicted risk. The error bars represent the binominal uncertainty equal to one standard error.

These factors may have implications for e.g. dose-sparing strategies in treatment planning. Existing NTCP models may not be suitable for predicting dysphagia more than five years after RT, and further efforts should be made to reduce the prevalence and consequences of this late effect in future HNC survivors.

## Statements & declarations

### *Author contributions*

KB, BBH, CEK and CDA conceived the idea, planned, and managed the project. ED, RSF, GLA, EM, and ÅH contributed to the study design. TTMH, TPH, GLA, BBH, and CDA collected the data. TTMH, ED, RSF, TPH, and CDA performed the analyses. All authors participated in the discussion and interpretation of the results. First draft of the manuscript was written by TTMH and CDA. All authors were involved in editing successive drafts and approved the final submitted version.

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### *Ethics approval*

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Regional Committees for Medical and Health Research Ethics (date 06/13/2018, reference 2018/1005), the local protocol committee (date 06/12/2018, reference 2018-21/22) and the Oslo University Hospital privacy office (date 05/29/2018).

### *Consent to participate*

Written informed consent was obtained from all participants before inclusion in the study.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2023.110044.

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